REMARKS

Reconsideration is respectfully requested in view of the following remarks and the enclosed Declaration Under 37 CFR § 1.132.

The claims presently pending before the Examiner are 16 – 24.

Claim Rejections under 35 USC § 102

Claims 16-18, 20, 21 and 24 were rejected under 35 USC 102(b) as being anticipated by Mifune et al. (US 3,846,551). This rejection is traversed.

As in the Office Action of January 4, 2011, the Examiner reiterates at page 4 that Mifune et al. *"disclose examples wherein a pyrethroid, cyclodextrin and piperonyl are well kneaded to form a paste (formulation example 7). Cyclodextrin complexes are known to form by kneading with other components (...) Therefore, the compositions according to Formulation Example 7 would comprise both the pyrethroid and the synergist complexed with cyclodextrin since they were well kneaded in the presence of cyclodextrin in water."*

The Examiner, in further supporting his rejection and in responding to the arguments of the Applicants, states that *"Mifune et al. disclose mixing an interacted compound of furamethrin and beta-cyclodextrin, PBO, stearic acid, SPAN 60, Tween 60 and water, wherein the mixture is well kneaded (formulation of Example 7), Mifune et al disclose sufficiently kneading the active with cyclodextrin and water in a kneader to prepare a cyclodextrin complex, wherein the suitable temperature range is 5-70°C and usually the kneading is carried out for about 30 minutes (column 4, line 1-19. Therefore, it is the position of the examiner that kneading a mixture of an interacted compound of furamethrin and beta-cyclodextrin with PBO in water will result in jointly complexing both the furamethrin and PBO with the CD."*

The Applicants respectfully traverse once again the rejection of the Examiner and, in order to support their arguments already filed in the previous Response, the Applicants file herewith a Rule 132 Declaration by Mr. Borzatta, who comments on the results of the

tests for the preparation of an inclusion complex by kneading a interacted complex of pyrethroid-beta-cyclodextrin and PBO, as per the Formulation in Example 7 of Mifune.

Formulation Example 7 of the cited reference illustrates that the preformed interacted compound of pyrethroid and the beta-cyclodextrin is mixed with piperonyl butoxide, stearic acid, Tween 60 and Span 60. Therefore the Mifune et al. reference describes that an initial complex is formed by the pyrethroid and the cyclodextrin and then kneading of this pre-formed (initial) complex with excipients and PBO lead to a paste formulation. According to Mifune et al., the interacted compound can be prepared in advance by intimately contacting the pyrethroid with the cyclodextrin as stated in column 5, lines 27-37.

The Applicants have already stated that the kneading of the interacted compound and PBO carried out under the conditions of Formulation Example 7 do not allow the joint complex to be obtained.

In order to show that the kneading process of Mifune did not achieve the joint complexation, Mr. Borzatta initially prepared the interacted compound as stated in Mifune in column 5, lines 27-37 and then kneaded it with PBO as per Formulation Example 7 of Mifune. For comparison purposes, Mr. Borzatta also followed the method of Example 6 of the present application in order to prepare the joint complex of pyrethroid-beta-CD-PBO. Specifically, Example 6 of the instant application refers to the formation of a joint complex of beta-cyclodextrin, PBO and bifenthrin.

The two samples which were obtained were then subjected to NMR analysis to ascertain the formation of the joint complex. As it can be clearly seen from Table 1 of the Rule 132 Declaration, it can be observed that the preparation of interacted complex of bifenthrin in beta-CD and subsequent kneading of the preformed complex with PBO as in Example 7 of US 3,846,551 gives four different chemical peaks, two of them characteristic of a complex formation (3.710 ppm and 3.650 ppm), with the other two peaks being characteristic of beta-CD proton without any complexation. This means there was a partial complexation of bifenthrin by using the kneading method, with free Beta-CD and free bifenthrin in the final sample.

By contrast, following the procedure for the joint complexation of bifenthrin and PBO according to Example 6 of the instant application, NMR data show that a complex was formed with *no free (uncomplexed) bifenthrin* and *no free (uncomplexed) beta-CD* present in the mixture.

In Table 2, the chemical shift of O-CH_2-O protons of PBO are shown. The chemical shift of 5.465 ppm is characteristic of free (uncomplexed) PBO.

As clearly shown in Table 2, by following the kneading procedure of Mifune, PBO is not complexed, while the complexation of PBO is present when the joint complex is formed in accordance with the claimed invention.

In summary, following the procedure indicated in Mifune et al, i.e. by kneading an interacted compound of pyrethroid in beta-CD with PBO, there is no joint complexation of PBO in beta-CD, which is contrary to the procedure recited in the claimed invention, according to which all the PBO present is complexed in beta-CD jointly to the pirethroid.

As a matter of fact, the lower efficiency of kneading versus the co-evaporation method for preparing an inclusion complex is well-known in the art (as already shown in the Response of June 30, 2011 with reference to *Veiga et al. J. Incl. Phenom. & Macrocycl. Chem.* 2005, 53, 77-83; in particular see page 81, Fig. 4 and right col. lines 10-23). In any event, according to the Mifune example there is absolutely no possibility for the formation of joint complexation of both PBO and pyrethroid in cyclodextrins.

Furthermore, Mifune neither teaches nor discloses that a joint complexation was achieved and nowhere in the entire Mifune specification is there any experimental evidence that a double inclusion complex of pyrethroid-PBO in CD is formed simply by means of kneading. Applicants have shown that the formation of an inclusion complex by kneading -under suitable operating conditions- CD, a pyrethroid and PBO in the presence of a suitable amount of water is both unlikely and unpredictable. A PBO inclusion complex cannot be obtained by kneading a pre-formed inclusion complex (having the cavities already occupied) in the presence of several other components (i.e. surfactants).

In view of the above, joint complexation was not achieved by Formulation Example 7 of Mifune. The situation is made even worse by the fact that according to Example 7, other excipients are present during the kneading process, i.e, stearic acid, Tween 60 and Span 60. As a matter of fact, according to the Examiner, the simple kneading of the interacted compound of pyrethroid and the beta-cyclodextrin with piperonyl butoxide and other excipients, i.e., stearic acid, Tween 60 and Span 60, at preferably 15-30°C, surely guarantees the formation of a joint complex of the sole pyrethroid-PBO-Beta_CD, therefore excluding that all the other joint complexes such as pyrethroid-strearic acid-Beta-CD, pyrethroid- Tween 60-Beta-CD, pyrethroid- Span 60 – Beta-CD can be formed or, alternatively, that during the kneading step at 15°C - 30°C, the pyrethroid exits from the cavity of beta-CD, thus allowing the entry of other components among piperonyl butoxide, stearic acid, Tween 60 and Span 60.

In view of the experimental data in the Rule 132 Declaration of Mr.Borzatta, and the foregoing arguments, the Applicants respectfully point out that the chemically-unfounded reasoning of the Examiner is clearly affected by an ex post-facto or hindsight analysis. Applicants respectfully submit that the Examiner has sought to find all the technical features of claim 1 in Mifune, but, clearly the most important feature, i.e. the joint complexation of PBO, pyrethroid and Beta-CD, is not found in Mifune.

Claim 16 and the claims dependent thereon, clearly distinguish over the teaching of Mifune. Since the Examiner has failed to establish a case of *prima facie* anticipation by a preponderance of the evidence, the rejection under §102(b) has been overcome and should be withdrawn.

Claim Rejections under 35 USC § 103

Claims 16-24 were rejected under 35 USC 103(a) as being anticipated by Biebel et al. (Int. J. Pharmaceutics 2003, 256, 175-181) and Szejtli (US 4,524,068). This rejection is traversed.

Biebel discloses complexation of pyrethrum extract with γ-cyclodextrin. Biebel also teaches that pyrethrins can benefit from the use of synergists, such as PBO. Biebel

also teaches that a synergist component may also profit from a complexation with cyclodextrins.

Szejtli teaches that a synergist (such as PBO) can be complexed with cyclodextrins resulting in increased solubility.

The Examiner acknowledges that *"Biebel and Szejtli do not explicitly disclose jointly complexing the pyrethrin or pyrethroid and the synergist with cyclodextrin, as instantly claimed"*. Therefore, the Examiner has failed to support a case of *prima facie* obviousness because he has failed to point out where this essential feature of **"joint complexation"** can be found in the two references. He has only referred to the combination of references to inappropriately derive this essential feature of the claimed invention.

Specifically, the Examiner states that Biebel et al teach complexation of pyrethrum extract with cyclodextrin and Szejtli teach that synergists may also profit from complexation and from this point derives that the joint complexation is suggested *prima facie*.

The combination of teachings of Biebel et al., (a pyrethrum can be complexed with cyclodextrin and the synergist can be complexed with cyclodextrin) at most may suggest to one of ordinary skill to arrive at a mixture of a pyrethrum/CD complex with a synergist/CD complex. This mixture suggested by the art is decidedly different and readily distinguishable from the claimed double inclusion complex.

Furthermore, even if Biebel suggests that pyrethrum can be complexed with cyclodextrin and the synergist can also be separately complexed with cyclodextrin, Biebel reported a ***negative result*** in the activity of pyrethrum when the synergist is also complexed.

Specifically, as indicated in Table 1 on page 177, formulations of pyrethrum complexed with γ-CD and synergist, wherein the synergist can be complexed or not in γ-CD, were prepared. The formulations were tested for insecticidal activity and the results are shown in Figure 3. As one of ordinary skill in the art would have immediately known from Figure 3, the activity of the pyrethrum and PBO when both are separately

complexed (Formulation XII) , is lower than the activity of formulation IX, wherein only the pyrethrum is complexed in cyclodextrin and the synergist is simply added to the mixture. The foregoing teaching would have been further underscored to a person of ordinary skill in the art from a consideration of Formulation VIII in the same Figure 3 containing the complex of pyrethrum with gamma-CD and the synergist and Formulations XI and XII containing pyrethrum and synergist both separately complexed. The foregoing is confirmed by considering Figure 4, wherein Formulation XV containing **both the pyrethrum and the synergist separately complexed is poorer in pesticidal activity** than formulation XIV containing only the pyrethrum complex and the synergist simply added to the mixture

As far as the teaching of Szejtli is concerned, this reference explains that the complex of PBO and cyclodextrin can increase the solubility of PBO, ***but never suggests to jointly complex pyrethrum and PBO***.

Therefore, the skilled person, even if he had known that the solubility of PBO can be increased by complexation in cyclodextrin, would not have used it in the already complexed mixture of pyrethrum, because **he knew of the poorer activity of the synergist-CD complex** with respect to the free synergist in the mixture from Biebel.

It becomes evident that the double inclusion complex of the claimed invention is neither suggested nor is it derivable from a combination of the teachings of Biebel and Szejtli. In addition, the unexpectedly improved insecticidal effectiveness of the claimed complexed composition cannot be said to be taught, disclosed or derivable from the cited references.

Furthermore, the differential release for better activity of the joint complex of the claimed invention is experimentally reported by Bingham G. et al., *Pest Manag. Sci.* 2007, 63, 276-281, which was attached to the response of June 30, 2011. The tests therein demonstrate that the claimed composition wherein both components (i) and (ii) are jointly complexed, is much more effective, far beyond any expectations of the person of ordinary skill in the art, with respect to a mixture of pyrethroids and synergist, even if they were separately complexed.

For all of the above reasons, claims 16-24 distinguish over the combination of Biebel and Szejtli. Since the Examiner has clearly failed to establish a case of *prima facie* obviousness by a preponderance of the evidence, the rejection under § 103(a) has been overcome and should be withdrawn.

CONCLUSIONS

In view of the above, Applicants believe that the Application as currently pending is in condition for allowance on the grounds that the arguments provided fully overcome the rejections raised in the outstanding Office Action.

Accordingly, Applicant respectfully solicits the issuance of a Notice of Allowance.

Please charge any fees which may be due and which have not been included herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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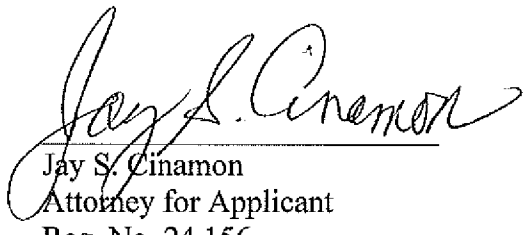
By 
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